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Gladys H. Monroy
Chiron Corporation
4560 Horton Street
Emeryville, CA 94608-2916

EXAMINER	
MOORE, WILLIAM W	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/884,456	HOUGHTON ET AL.	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed on 12 February 2007 in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12 February 2007 has been entered. Claims 27-43 are not amended and remain in the application. This communication is not made final because a new ground of rejection is stated herein,

Double Patenting: Non-Statutory

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-44 are rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017. While Applicant states at page 6 of the Response that a terminal disclaimer will be filed upon an indication of allowable subject matter herein, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

This is a new ground of rejection, replacing the corresponding rejection of record where it affects more claims of the instant application. Claims 27-43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8-12, 14 and 15 of copending application 10/438,313. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the copending reference claim because the examined claim is either anticipated by, or would have been obvious over, the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 27-43 are obvious over claims 1-6, 8-12, 14 and 15 of the copending application and, as such, the conflicting claims are not patentably distinct from each other where claims 1-6, 8-12, 14 and 15 of the copending application and claims 27-43 herein and are both directed to polynucleotides or expression vectors encoding HCV proteases or fusion proteins thereof. While the instant claims and the copending differ in the scope of the polynucleotides or expression vectors encoding HCV proteases or fusion proteins thereof that they encompass, the portion of the specification in 10/438,313 that supports the recited genus of polynucleotides or expression vectors encoding HCV proteases or fusion proteins includes an embodiment that would anticipate all of claims 27-43 herein, e.g., the polynucleotides or expression vectors encoding the protease of SEQ ID NO:65 or fusions thereof to human superoxide dismutase. Claims 27-43 cannot be considered patentably distinct over claims 1-6, 8-12,14 and 15 of copending application 10/438,313 when there is a specifically recited embodiment that would anticipate claims 27-43 herein.

Alternatively, claims 27-43 cannot be considered patentably distinct over claims 1-6, 8-12,14 and 15 of copending application 10/438,313 when there is a specifically disclosed embodiment in 10/438,313 that supports claims 27-30 of that copending application and falls within the scope of claims 1-6, 8-12, 14 and 15 herein because it would have been obvious to one having ordinary skill in the art to modify the polynucleotides or expression vectors of claims 1-6, 8-12, 14 and 15 of copending application 10/438,313 by selecting a specifically disclosed embodiment that supports those claims, i.e., polynucleotides or expression vectors encoding the protease of SEQ ID NO:65 or fusions thereof to human superoxide dismutase. One having ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within the genus of claims 1-6, 8-12, 14 and 15 of copending application 10/438,313.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments at pages 6-16 of the Response filed 12 February 2007 have been fully considered but are not deemed to be persuasive to overcome the rejection of record. Applicant suggests that the specification adequately describes claimed compositions comprising polypeptides that include a hepatitis C virus [HCV] NS3 domain protease, or an active truncation analog thereof, and an assay utilizing the protease, whether the protease structure comprises a generic HCV NS3 domain protease of claims 27, 31 and 36, or comprises at least the amino acid sequence of SEQ ID NO:65, or an active NS3 domain HCV protease truncation analog thereof", of claims 28-30 and 33-35. The Federal Circuit has said that a sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by nucleotide sequence or recitation of structural features common to members of the genus and constituting a substantial portion of the genus. In the instant application a genus of DNAs is defined by a representative number of proteins encoded by polynucleotides of the claims and a protein is defined either by amino acid sequence or by a recitation of structural features common to members of the genus of proteins and constituting a substantial portion of that genus which can sufficiently describe the genus. As discussed in the USPTO Written Description guidelines, the written description requirement for a claimed genus may be satisfied through (1) sufficient description of a representative number of species by actual reduction to practice, (2) reduction to drawings, (3) disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, (4) functional characteristics coupled with a known or disclosed correlation between function and structure, or (5) a combination of such identifying characteristics sufficient to show Applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus and one must describe a sufficient variety of species to reflect the variation within the genus where there is substantial variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus embracing widely variant species cannot be achieved by disclosing one species within the genus.

Applicant asserts at page 7 of the Response that an "NS3 domain HCV protease" encoded by polynucleotides comprised by compositions of claims 27-36 and 44, and expression vectors

of claims 37-43 comprising such encoding polynucleotides, will "comprise[ ] both the NS2/3 protease activity disclosed in Example 5 and the NS3 serine protease activity disclosed . . . in Examples 10 and 11." Indeed, publications in the art subsequent to the date of Applicant's disclosure show that the breadth of Applicant's claims encompasses both an HCV NS2/3 metalloprotease and an HCV NS3 serine protease as well as any proteases comprising active fragments of either. The claims are not limited, however, to a species representing the necessary common attributes or features of the HCV NS3 serine protease that the specification describes, i.e., SEQ ID NO:65 and the p600, p500 and p300 polynucleotide constructs, or active fragments thereof. Example 5 of the specification purports to show a working example of HCV protease activity, now argued by Applicant to be an example of HCV NS2/3 protease activity, but the evidence is clear that cleavages of the proteins encoded by the P600, P500 and P300 polynucleotide constructs in Example 5 cannot be mediated by an HCV-derived protease where these polynucleotide constructs encode proteins that contain neither an NS3 serine protease cleavage site nor all of residues essential for HCV NS2/3 metalloprotease cleavage at the NS2/3 junction found within proteins encoded by these constructs. With regard to a stand-alone NS3 domain serine protease activity, Applicant cites publications by Lin et al., Sardana et al., Vishnuvardan et al. and Barbato et al., at pages 9 and 10 of the Response to support the assertion that an NS4A peptide – a feature that the disclosed p600, p500, p300 and p190 polynucleotide constructs all lack and that the specification does not otherwise disclose or suggest – is "not a necessary factor for NS3 serine protease activity". This is not persuasive because the experiments of Cindy Lee and others show that the portion of the NS3 serine protease within the proteins encoded by Applicant's disclosed polynucleotide constructs, such as polynucleotides of claims 27-36 and 44, and expression vectors of claims 37-43 comprising such polynucleotides, unquestionably cannot mediate the cleavage activity disclosed by the specification because mutation of the active site serine residue did not eliminate the cleavage.

Applicant argues at pages 14-6 of the Response that one of skill in the art would have understood the "34 kDa band" of Example 5 to correspond to the product of a NS2/3 protease-specific cleavage from the consistent observation of a 34 kDa band reactive with anti-HCV antisera described in Example 5 of the specification, corresponding to the active fusion proteins p300, p500, and p600, where the band does not appear with the inactive p190 fusion. Applicant points to the fact that it is known in the art that some proteins exhibit anomalous migration on SDS polyacrylamide gels and cites a few examples of such. However, this is not persuasive as such anomalous migration of a protein is in fact the exception, not the rule. Absent evidence to the contrary, a skilled artisan would expect that a SDS-PAGE protein band corresponding to a

molecular weight of 34 kDa in fact consists of a protein having a molecular weight of approximately 34 kDa. When a skilled artisan suspects that a band may in fact be running anomalously but that, as is the case here, other explanations of inconsistent molecular weight exist, additional experimental evidence is generally presented to show that the observed band is in fact the protein the artisan believes it is. There is no evidence within the specification, the art, nor the declarations of Dr. Weiner or Dr. Ou submitted on 12 February 2007, that the "34 kDa band" of Example 5 is in fact a cleavage product of the p300, p500, and p600 fusion proteins **produced by a specific cleavage mediated by the NS2/3 protease**, i.e., a protein fragment with an actual molecular weight of 24 kDa, instead of a cleavage product of these fusion proteins by a bacterial protease at some other site(s) which produce a protein fragment of approximately 34 kDa. While the reactivity of this band with HCV antisera shows that the band does correspond to an HCV fragment of the fusion proteins there is no evidence of record to suggest that it is a fragment produced by HCV NS2/3 protease cleavage between residues 1026 and 1027 of the HCV polyprotein. The mere possibility that anomalous migration might have occurred is not enough for the skilled artisan to reasonably conclude that this is what did occur in the instant situation.

Applicant argues at pages 11-13 of the Response, citing the declaration of Dr. Ou and the second declaration of Dr. Weiner, that one of skill in the art, upon review of the specification, would understand that fusion of the heterologous hSOD polypeptide sequence to a truncated HCV NS2/3 protein that by itself is inactive, had restored the activity of the NS2/3 protease. Applicant points to two instances where fusion of a heterologous protein to an inactive enzyme produced an active enzyme at page 12 of the Response and two instances where the HIV-1 protease retains activity when fused to a heterologous protein at page 13 of the Response. This falls short of suggesting that that fusion of the hSOD sequence to residue 946 of an HCV NS2/3 protease fragment that, by itself, is inactive might have restored HCV NS2/3 protease activity. This is because one instance cited at page 12 of the Response is an unexpected exception and does not involve a protease and because the HIV-1 protease of the fusions cited in the other three instances cited at pages 12 and 13 of the Response is not the HCV NS2/3 protease and is not structurally related to the HCV NS2/3 protease. In addition, Applicant provides nothing to show that this is, in fact, what occurs in Example 5 of the specification. While unexpected phenomena do occur, they clearly require corroboration before they can be taken as fact and there is no such corroboration in the present record. As such, the much more plausible explanation of the phenomenon seen in Example 5, i.e., the activity of a bacterial protease, is considered to be the basis for the cleavage disclosed in the specification. While the declaration

of Dr. Weiner states that one of skill in the art would understand that fusion of the heterologous hSOD polypeptide sequence to the truncated NS2/3 fragments restored activity of the NS2/3 protease, there is no evidence or scientific reasoning provided to support a statement that the observed activity is necessarily that of an HCV NS2/3 protease. What a skilled artisan would understand from the disclosure of the specification is that the p300, p500, and p600 fusion proteins were cleaved, and that the p190 fusion protein was not cleaved, but would find no evidence therein as to the nature of the protease producing the cleavage nor even evidence of the site within the fusion protein where the cleavage occurred other than the size of the fragment on the SDS gel which fails to agree with what one would expect from a cleavage at the NS2/3 cleavage site as discussed above. Instead, the only available evidence as to what protease produced the cleavage, i.e., the size of the cleavage fragment produced, leads away from a conclusion that the cleavage was produced by a HCV NS2/3 protease. Applicant is trying to prove that Example 5 demonstrates HCV NS2/3 protease activity by declaring that Example 5 shows NS2/3 protease activity without any evidence or reasoning in support. For all the reasons discussed above the rejection of record is maintained.

Claims 27-36 remain rejected for reasons of record 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable the preparation of polynucleotides that encode proteins, including the P600, P500, P300 and P190 proteins, that comprise an HCV-specific protease activity, or generic versions thereof, or active truncation analogs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments at pages 17-21 of the Response filed 12 February 2007 have been fully considered but are not deemed to be persuasive to overcome the rejection of record. Applicant suggests that no undue experimentation would be required of one of ordinary skill in the art to prepare polynucleotides of the claims encoding HCV NS3 proteases, or expression vectors comprising such polynucleotides, where an HCV NS3 protease is encoded by any of the P600, P500, P300 or P190 polynucleotide constructs or comprises "more than the HCV amino acid sequence region present in SEQ ID NO:68, or a generic version thereof, or an active truncation analog thereof". With regard to what may constitute "undue experimentation", the CCPA, the precursor of the Court of Appeals for the Federal Circuit, determined that a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of the guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). In considering whether or not the scope of the guidance provided in the instant specification is enabling, it is

not necessary to reach the broader embodiments embraced by a generic HCV NS3 domain protease and "an active truncation analog thereof" because the teaching of the specification that the amino acid sequence of SEQ ID NO:65, encoded by polynucleotides of claims 31 and 36, where such a polynucleotide is present in an expression vectors of claim 41, may constitute an HCV NS3 domain protease cannot be combined with the state of the art at the time the specification was filed to permit the preparation of a claimed protease-encoding polynucleotide by an artisan at that time without undue experimentation. This is because the specification teaches that the amino acid sequence of SEQ ID NO:65 is the core of a claimed protease but teaches no substrate that can be cleaved by a protease of SEQ ID NO:65, which consists of residues 1005-1204 of the HCV polyprotein. While SEQ ID NO:65 includes all residues necessary for NS3 domain serine protease cleavage at the NS5A/5B junction, it does not include the amino acid sequence regions necessary either for NS2/3 metalloprotease cleavage at the NS2/3 junction or for NS3 serine protease cleavage at any of the NS3/4A, NS4A/4B or NS4B/5A junctions. Indeed, the substrates actually taught in the specification are not substrates of a NS3 domain serine protease of SEQ ID NO:65.

A. At page 20, lines 14-19, the specification states, "[a]s the HCV protease is believed to cleave itself from the genomic polyprotein, one can employ this auto-catalytic activity both to assay expression of the protein and determine activity. For example, if the protease is joined to its fusion partner so that the HCV protease N-terminal cleavage signal (Arg-Arg) is included, the fusion product will cleave itself into fusion partner and active HCV protease."

B. The specification continues, page 20, line 21, through page 21, line 3, "[i]t is presently preferred to employ small peptide p-nitrophenyl esters or methylcoumarins, as cleavage may then be followed by spectrophotometric or fluorescent assays. Following the method described by E. D. Matayoshi et al., Science (1990) 247:231-35, one may attach a fluorescent label to one end of the substrate and a quenching molecule to the other end: cleavage is then determined by measuring the resulting increase in fluorescence. If a suitable enzyme or antigen has been employed as the fusion partner, the quantity of protein produced may easily be determined. Alternatively, one may exclude the HCV protease N-terminal cleavage signal (preventing self-cleavage) and add a separate cleavable substrate, such as a fragment of the HCV NS3 domain including the native processing signal or a synthetic analog."

C. The specification next teaches, page 21, lines 9-19, that "[t]hree of the putative cleavage sites of the HCV polyprotein have the following amino acid sequences: Val-Ser-Ala-Arg-Arg//Gly-Arg-Glu-Ile-Leu-Leu-Gly (SEQ ID NO:36), Ala-Ile-Leu-Arg-Arg//His-Val-Gly-Pro (SEQ ID NO:88) and Val-Ser-Cys-Gln-Arg//Gly-Tyr (SEQ ID NO:89). These sites are characterized by the presence of two basic amino acids immediately before the cleavage site, and are similar to the cleavage sites recognized by other flavivirus proteases".

These most specific teachings of the specification thus suggest that a skilled artisan use as substrate either (i) a fusion of the N-terminus of SEQ ID NO:65 with a fusion partner, (ii) a

fluorescently labeled peptide comprising a dibasic residue, or (iii) the peptides of SEQ ID NOs:36, 88 or 89. To the contrary, the current state of the art clearly shows that none of the compounds suggested by the specification can be cleaved by the HCV NS3 domain serine protease of SEQ ID NO:65. The amino acid sequence of SEQ ID NO:65 includes only a single HCV polyprotein cleavage site, the NS2/3 junction, but this junction is cleaved only by the NS2/3 metalloprotease and not by the NS3 serine protease. See, e.g., Hijikata et al., J. Virology 67(8): 4665-4675, Grakoui et al., PNAS 90:10583-10587, and Grakoui et al., Ref 467, Eckart et al., Ref 427, and Komodo et al., Ref 562, all of record. Furthermore, the cleavage site specificity of the NS3 domain serine proteinase is not for peptides with dibasic residues, or even single basic residues, but for the sequence D/E-X-X-X-X-C/T-S/A. See Komodo et al., Ref 562, and Grakoui et al., Ref 467. Cleavage at non-natural sites in the HCV polyprotein has not been observed. See Grakoui et al., Ref 467. Indeed, efficient cleavage at all of the natural cleavage sites except the NS5A/5B junction, requires an additional HCV peptide, termed NS4A. See Failla et al., Ref 433, and Lin et al., Ref 601. The NS4A cofactor is not present within SEQ ID NO:65, thus such a protease is highly unlikely to cleave non-natural substrates with non-consensus cleavage sites as even the best substrates are cleaved inefficiently absent the NS4A cofactor.

Claims 27, 31, 32, 33, 37, and 42-44 reach compositions, and expression vectors, that comprise polynucleotides encoding any HCV NS3 domain protease, whether or not it is part of a fusion polypeptide, while claims 28-31 and 34-36 and 38-41 reach HCV NS3 domain proteases, whether or not part of a fusion polypeptide, that comprise compositions, and expression vectors, that comprise polynucleotides encoding any of SEQ IDs NOs:1, 63, 64, or 65. The specification fails to teach one of skill in the art either (1) how to make any active fragment of the NS2/3 metalloprotease or (2) how to make an active fragment of the NS3 domain serine protease for the same reasons discussed above that the specification fails to teach how to use SEQ ID NO:65. The specification fails to teach how to make the NS2/3 metalloprotease where it lacks any teaching of the residues of the HCV polyprotein essential to this protease activity and lacks any suggestion that this enzyme even exists. As discussed in the rejection for inadequate written description above, NS2/3 metalloprotease activity requires HCV residues not found in SEQ ID NO:65 and not present in the specific proteins encoded by polynucleotide constructs of P600, P500, and P300 which the specification implies are active proteases with autocatalytic cleavage activity. There is no noticeable homology of a protease that comprises the amino acid sequence of SEQ ID NO:65 to any metalloprotease known at the time the specification was filed that would have guided a skilled artisan to include these additional, necessary, residues. The specification teaches away from doing so in suggesting that a protease encoded by

polynucleotides of the claims herein is a serine protease encompassed within SEQ ID NO:65 and within proteins encoded by the specific polynucleotide constructs of P600, encoding residues 946-1630 of the HCV polyprotein, P500, encoding residues 946-1457, and P300, encoding residues 946-1245, where two of the three catalytic residues of the serine protease catalytic triad, serine and histidine, are in the amino acid sequences of SEQ ID NOS:64 and 63, respectively.

Neither does the specification provide any working example of HCV protease activity. While Example 5 of the specification purports to show such working examples, the evidence is clear that cleavages of the proteins encoded by the P600, P500 and P300 polynucleotide constructs in Example 5 are not mediated by an HCV derived protease as these constructs encode proteins that contain neither an NS3 serine protease cleavage site nor all residues essential for NS2/3 metalloprotease cleavage of the NS2/3 junction found within the encoded proteins. Furthermore, the experiments of Cindy Lee and others clearly show that the cleavage activity seen in these experiments unquestionably cannot be mediated by an NS3 domain serine protease encompassed within proteins encoded by the polynucleotide constructs where mutation of the active site serine residue did not eliminate cleavage. Thus the only reasonable explanation of cleavages of the P600, P500 and P300-encoded proteins reported in Example 5 is that they were the result of the activity of a protease present in the bacterial host cell in which the polynucleotide constructs were expressed.

Applicant argues at pages 17-18 of the Response that Example 5 of the specification teaches how to make an active NS2/3 protease by fusing a peptide having the sequence of Figure 1, or a truncation analog thereof, with an hSOD protein "to demonstrate its auto-catalytic activity". Yet the HIV protease fusions cited at page 18 of the response do not comprise a metalloprotease similar to the HCV NS2/3 protease and there is absolutely no evidence yet in the record that the polynucleotide constructs of Example 5 encode an active NS2/3 protease, i.e., capable of cleaving the NS2/NS3 boundary at residues 1026/1027 of the HCV polyprotein. Instead, there is substantial evidence in the record to suggest that these polynucleotide constructs are not capable of encoding a protease that cleaves at the NS2/NS3 boundary at residues 1026/1027 of the HCV polyprotein. Hijikata et al., J. Virology 67(8): 4665-4675, Grakoui et al., PNAS 90:10583-10587, Grakoui et al., Ref 467, Santolini et al., Ref 741, disclose that region of residues 898-946 of the HCV polyprotein is essential for activity of the NS2/3 metalloprotease and all of the proteins encoded by polynucleotide constructs of Example 5 lack the region comprising these residues. While Applicant suggests that the hSOD fusion partner in fusion polypeptides encoded by these polynucleotide constructs recreated an active NS2/3

protease from an inactive fragment of the NS2/3 protease, Applicant provides no evidence for the record supporting this position. See the discussion above. It is noted that even if the proteolytic activity observed in Example 5 was in fact a NS2/3 protease activity recreated from an inactive fragment of the NS2/3 protease by fusion of the hSOD sequence thereto, the polynucleotide constructs of Example 5 are not working examples of polynucleotides encoding a NS2/3 protease within the scope of the claims pending herein where each of these claims requires the presence of an active HCV NS3 domain protease truncation analog in an encoded polypeptide, i.e., this portion of the protease derived from the HCV polyprotein itself must have proteolytic activity.

The polynucleotide constructs of Example 5 clearly do not include an active NS2/3 protease truncation analog and approach the limitations of the claims herein only in that they include an HCV NS3 serine protease truncation analog that, while active in contexts the specification does not disclose, could not have mediated cleavages observed for proteins encoded by Example 5's P600, P500 and P300 polynucleotide constructs. The specification lacks any teaching of how to make a NS2/3 metalloprotease, lacks any suggestion that a NS2/3 metalloprotease exists, and fails to teach any residues of the HCV polyprotein that are essential to NS2/3 metalloprotease activity. No noticeable homology between the essential residues of the NS2/3 metalloprotease and the amino acid sequences of other metalloproteases was known at the time the instant specification was filed that could have guided the skilled artisan to include residues 898-946 of the HCV polyprotein in a protease of the claimed invention and the specification clearly teaches away from doing so by suggesting that the protease disclosed is a serine protease having its catalytic serine and histidine residues of the serine protease catalytic triad within the sequences of SEQ ID NOS:64 and 63 respectively. It is noted that Applicant also argues that fusing the amino acid sequence of a protein of interest to the amino acid sequence of human superoxide dismutase (hSOD) was an established method of achieving high-level expression of a stable fusion protein as of the filing date of the parent application, but this is not persuasive. While fusion technology was a known means of producing high-level expression of proteins or protein fragments which exhibit a desired activity by themselves, or of stabilizing a desired protein having a desired activity which, alone, is highly susceptible to protease degradation, it was not a known means of adding a protease activity to a protein lacking that activity.

Applicant separately argues at pages 18-20 of the Response that page 20, lines 14-16, of the specification teaches how to use the NS3 domain serine protease, in the absence of any disclosure of a suitable substrate for this protease, by using a full-length HCV polyprotein as a substrate. This is not persuasive because the argument mischaracterizes the disclosure of this

portion of the specification: Page 20, lines 16-19, states, "As the HCV protease is believed to cleave itself from the genomic polyprotein, one can employ this auto-catalytic activity both to assay expression of the protein and determine activity. For example, if the protease is joined to its fusion partner so that the HCV protease N-terminal cleavage signal (Arg-Arg) is included, the fusion product will cleave itself into fusion partner and active HCV protease." This passage suggests using **fusion proteins** including the HCV protease N-terminal cleavage signal rather than the entire genomic polyprotein, thus the argument at pages 18-20 of the Response attempts to remove lines 14-16 at page 20 of the specification from the context of the following discussion at lines 16-19 at page 20. Even alone, lines 16-19 merely suggest that an expected autocatalytic activity can be used to provide substrates, i.e., using any fragment including both the protease and bordering HCV sequences, which include the cleavage site, rather than the use of the entire genomic polyprotein. Furthermore, this particular passage teaches away from use of a suitable substrate by suggesting using HCV fragments including the N-terminal cleavage signal, i.e., the N-terminal boundary of the NS3 domain, which in fact is not a substrate for the NS3 domain serine protease. Nothing in the specification guides a skilled artisan to identify suitable HCV fragments that include a NS3 serine protease cleavage site.

Applicant suggests that viral polyprotein substrates for assaying proteases were commonly used in the art at the time of the invention, citing eight articles in support of this position. Yet the cited articles do not in fact support Applicant's position. Of the eight articles submitted, seven do not in fact teach using an entire genomic polyprotein of the virus in question and instead teach the use a fragment that is a smaller portion thereof. By way of example, Nicklin et al. use only the 1ABCD fragment of a poliovirus genomic polyprotein, all three of Yoshinaka et al. use the MSV $Pr65^{gag}$ portion of the entire gag-pol-env polyprotein, while Krausslich et al. and both of Pichuates et al. use the HIV $Pr53^{gag}$ portion of the HIV gag-pol-env polyprotein. In each of these references the polyprotein used is naturally cleaved into no more than 4 peptide fragments while the entire HCV genome is cleaved into many more than this. The art clearly would have taught away from using a substrate that is cleaved into numerous products as the large number of potential products makes analysis difficult. In many of the references Applicant cites, including the eighth article, by de Groot et al., there is frequently difficultly in analyzing the presence or absence of cleavage of the polyproteins used where these proteins are cleaved into many fewer products. See, e.g., Figures 1-5 of de Groot et al, Figures 1 and 2 of Yoshinaka et al., PNAS, Figure 1 of Yoshinaka et al., J. Virol, 1985, and Figure 2 of Krausslich et al. The art and Applicant's specification recognize that the best substrates are small peptides that have no protease activity themselves and include but a single cleavage site in which the products of

cleavage are easily distinguished from the uncleaved substrate. The HCV polyprotein clearly does not meet these requirements, thus the state of the art would have guided a skilled artisan away from its use. None of the guidance provided by the specification would have led a skilled artisan to a suitable substrate for SEQ ID NO:65 and would instead have led a skilled artisan down a futile path.

Applicant also suggests at page 21 of the Response that use of a genomic HCV polyprotein as a substrate for proteolysis would compensate for the absence from the disclosure of any teaching that the NS3 domain serine protease may function, in some context, without the NS4A cofactor. The issue, however, is that of undue experimentation where even the best substrates are cleaved inefficiently in the absence of the NS4A cofactor and there is some disagreement in the art as to which of the natural cleavage sites can be cleaved by the NS3 serine protease in the absence of NS4A cofactor, a disagreement likely due to differences in the exact conditions of the various assays in the subsequent art. In every case Applicant cites, cleavage is substantially more efficient in the presence of the cofactor and the specification provides no guidance for selecting a substrate including a natural cleavage site cleaved in the absence of the NS4A cofactor. The specification provides absolutely no guidance for determining the limited number of specific sequences, from 1-3 depending on the conditions under which the assay is performed. For all the reasons discussed above the rejection of record is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant' arguments at pages 21-23 of the Response filed on 12 February 2007 have been fully considered but are not deemed to be persuasive to overcome the rejection of record. In response to the first rejection of record, Applicant suggests at pages 21 and 22 that one of skill in the art would understand that a polynucleotide encoding a "NS3 domain hepatitis C virus ... protease truncation analog" must necessarily encode a polypeptide possessing a "proteolytic" activity, that the "NS3 domain of HCV is characterized by the sequence of Figure 1 (SEQ ID NO: 70)" and that the specification, at page 8, lines 1-3, "describes a truncation analog as: 'the sequence may be substantially truncated, particularly at the carboxy terminus, apparently with full retention of protease activity'". Yet claims 27, 32, 33, 37, and 42-44 make no reference to Figure 1, or any sequence identifier, that might provide a structure that permits the artisan and

the public, seeking to determine the metes and bounds of the intended subject matter, to determine what is, or is not, a "truncation analog" by identifying either an amino-terminus or a carboxyl terminus from which (a) truncation(s) might begin. Applicant's argument affects claims 28-31, 34-36, and 38-41 as well in asserting, essentially, that protease activity equally identifies both an integral NS3 domain hepatitis C virus protease and all conceivable truncation analogs embraced by encoding polynucleotides of the claims, a clear admission that the claims fail to describe a definite, initial, structure that allows the artisan and the public, seeking to determine the metes and bounds of the intended subject matter, to ascertain whether the claims are drawn only to polynucleotides that encode proteases within the boundaries of the NS3 domain or embrace polynucleotides that encode proteases that include the entire NS3 domain. Applicant then discusses Figure 1 and SEQ ID NO:1 of the specification, and a "functionally minimal domain" identified in the two Declarations submitted with the Response, at page 22 of the Response. The specification states however, at page 6, lines 22-24, that "[t]he term "HCV protease" refers to an enzyme derived from HCV which "exhibits proteolytic activity, specifically the polypeptide encoded in the NS3 domain of the HCV genome" and page 7, lines 23-26, states: "[f]urther, the actual N and C termini may vary, as the protease is cleaved from a precursor polyprotein: variations in the protease amino acid sequence can result in cleavage from the polyprotein at different points. Thus the amino- and carboxy-termini may differ from strain to strain of HCV." The pending claims can be construed in view of these passages to identify HCV NS3 proteases as those naturally produced by an HCV strain upon cleavage of the HCV polyprotein at the boundaries of the NS3 domain of that particular strain but Applicant argues instead at page 22 of the Response that such proteases may be a "functionally minimal domain" identified in Declarations submitted with the Response. The preceding arguments in the Response addressing the rejections of record of claims herein under the first paragraph of the statute suggest that such a protease must a portion extending beyond the amino-terminal boundary of a native NS3 domain to include an undefined amino acid sequence region of an amino-proximal fusion partner that contributes to, and activates, protease activity. The rejection of record is therefore maintained and is best addressed by amending claims 27, 32, 37 and 44 to state the nature of the intended protease activity and to require that some particular structure of the disclosed NS3 domain be present in protease-encoding polynucleotides of compositions and vectors of claims 27, 32, 33, 37 and 42-44 that is also present in polynucleotides and vectors of claims 28-31, 33-36, and 38-41 lest they become improperly dependent claims.

Claims 27-31 are independently rejected for reasons or record as indefinite in view of the recitation of the phrase, "consists essentially of", in claim 27. Applicant argues at pages 22 and

23 of the Response that the claims be considered to describe a "dominant [coding] component" and to encode other components, citing *PPG Industries v. Guardian Industries*, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). The polynucleotides and vectors of the claims are not compositions of matter that have "listed ingredients" and that are open as well to "unlisted ingredients that do not materially affect the basic and novel properties" of the stated "ingredient". Instead, each rejected claim necessarily describes a polymer within which each nucleotide is covalently bonded to at least one other nucleotide, and a resulting polynucleotide can have no physically separate, lesser, component, thus cannot "consist essentially of" one component. Claims 28-31 are included in the rejection because they do not resolve the ambiguity of claim 27 from which they depend. Appropriate transitional terms for describing the intended polymer subject matter were suggested in the rejection of record: "comprises", "has", and "consists of". Amending claim 27 to state, e.g., "comprising" will overcome this rejection.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
26 April 2007